COMMUNICATION

A chemoenzymatic synthesis of the styryllactone (+)-goniodiol from naphthalene

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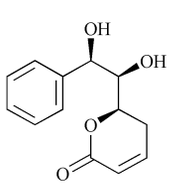
The enantiomerically pure *cis*-1,2-diol 2, which is obtained by microbial oxidation of naphthalene, has been converted, *via* a sequence of reactions including oxidative C–C bond cleavage, decarbonylation and ring-closing metathesis steps, into the natural product (+)-goniodiol (1).

(+)-Goniodiol (**1**) was first isolated from the leaves and twigs of the Asian tree *Goniothalamus sesquipedalis*,[1] and is a representative member of the styryllactone class of natural product, many of which show potent and selective cytotoxic properties.[2] For example, the title compound exhibits significant toxicity against the human lung carcinoma cell line A-549 (ED_{50} 0.122 μg mL^{-1}) whilst showing no such effects in a brine shrimp assay (LC_{50} > 500 μg mL^{-1}). As a consequence, various groups have developed useful synthetic approaches to the styryllactones with a particular emphasis having been placed on goniodiol (**1**), partly because a variety of its natural congeners are readily derived from this source. Two basic strategies have emerged. The first employs the chiron approach, as reported by Honda and co-workers[3] [using 2,3-*O*-isopropylidene-D-glyceraldehyde], Surivet and Vatéle[4] [using (*R*)-(−)-mandelic acid †] and Ley and co-workers[5] [using *S*-(−)-glycidol †]. The second exploits stoichiometric and catalytic asymmetric induction methodologies as described by Vatéle and co-workers[6] (chiral auxiliary-mediated nucleophilic addition to benzaldehyde), Mukai and co-workers[7] (chiral auxiliary-mediated nucleophilic addition to benzaldehyde) and Yang and Zhou[8] (Sharpless asymmetric epoxidation of cinnamyl alcohol). Herein we report a third approach to (+)-goniodiol (**1**), namely a chemoenzymatic synthesis which employs the enantiopure 1,2-dihydronaphthalene diol **2**[9] as a starting material. Although compound **2** is available in kilogram quantities *via* microbial dihydroxylation of naphthalene, the present work provides the first example of its exploitation in natural product synthesis.



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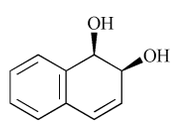

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The reaction sequence begins (Scheme 1) with the conversion, under standard conditions, of diol **2** into the corresponding and previously reported[10] acetonide **3** (99%). Oxidative cleavage of the double bond associated with the latter was achieved using OsO_4–$NaIO_4$ and the resulting unstable dialdehyde was immediately reduced to the diol **4**‡ {46% from **3**, $[\alpha]_D = -80 \times 10^{-1}$ deg cm^2 g^{-1} (*c* 3.0)§} using $NaBH_4$ in methanol. The benzylic alcohol moiety within compound **4** was selectively oxidized using manganese dioxide[11] so as to give the benzaldehyde **5** (73%). Since this latter compound was especially prone to acetonide group migration it was immediately acetylated thus affording the stable product **6** {53% from **4**, $[\alpha]_D = -236 \times 10^{-1}$ deg cm^2 g^{-1} (*c* 5.7)}. Decarbonylation of compound **6**, so as to generate compound **7** and thereby excise the single superfluous carbon associated with the starting material **2**, could be effected with Wilkinson's catalyst [$RhCl(PPh_3)_3$] in refluxing xylene.[12] However, stoichiometric quantities of this "catalyst" were required because the resulting carbonyl–metal complex is stable and does not, therefore, "turn over" (addition of diphenyl phosphorazidate proved ineffective[13]). To circumvent such difficulties, bis[1,3-bis(diphenylphosphino)propane]-rhodium tetrafluoroborate [$Rh(dppp)_2^+BF_4^-$],[14] a species known to effect decarbonylation of aromatic aldehydes, was used instead and the target **7** (76% at 64% conversion) was thereby obtained using only 10 mol% of the metal complex. Hydrolysis of acetate **7** with potassium carbonate in methanol afforded the corresponding alcohol **8** {93%, $[\alpha]_D = -84 \times 10^{-1}$ deg cm^2 g^{-1}(*c* 3.7, MeOH)} which was oxidized to the unstable aldehyde **9** using TPAP–NMO.

Allylation of compound **9**, as required for introduction of one of the two terminal double bonds that would participate in a ring-closing metathesis (RCM) so as to form the α,β-unsaturated lactone ring of target **1**, proved difficult to perform with the appropriate levels of stereocontrol. Of the various reagents and conditions examined[15–19] the most effective proved to be those involving allyltributylstannane in the presence of lithium perchlorate[16] and it is presumed this reaction is proceeding under conditions of chelation control.[20] Whilst the resulting *ca.* 2.7 : 1 mixture of compounds **10** {$[\alpha]_D = -56 \times 10^{-1}$ deg cm^2 g^{-1} (*c* 0.5)} and **11** {$[\alpha]_D = -32 \times 10^{-1}$ deg cm^2 g^{-1} (*c* 1.4)} (70% combined yield from **8**)¶ could be separated by HPLC, for preparative purposes it was more convenient to immediately subject this mixture to acylation with acrylic anhydride in the presence of DMAP. In this manner the corresponding mixture of acrylates **12** {mp = 36–38 °C, $[\alpha]_D = -11 \times 10^{-1}$ deg cm^2 g^{-1} (*c* 0.6)} and **13** {mp = 42–43 °C, $[\alpha]_D = -95 \times 10^{-1}$ deg cm^2 g^{-1} (*c* 1.1)} (*ca.* 50% combined yield) was obtained. In keeping with the behaviour[21] of many other acrylates derived from homoallylic alcohols, these compounds readily participated in a ring-closing metathesis (RCM) reaction when treated with 10 mol% of $(Cy_3P)_2Cl_2Ru$=CHPh (Grubbs' "first generation" catalyst)[22] in dichloromethane at ambient temperatures. The ensuing pyranones **14** {79%, mp = 137–138 °C, lit.[8] mp = 133–134 °C, $[\alpha]_D = -95 \times 10^{-1}$ deg cm^2 g^{-1} (*c* 0.5, EtOH), lit.[8] $[\alpha]_D = -100 \times 10^{-1}$ deg cm^2 g^{-1} (*c* 0.9, EtOH)} and **15** {73%, mp = 97–98 °C, $[\alpha]_D = -27 \times 10^{-1}$ deg cm^2 g^{-1} (*c* 0.4)} were readily separated by flash chromatography on silica gel. The spectroscopic data obtained on the former product matched those derived from authentic material.[5,8] Deprotection of compound **14** with aqueous acetic acid at 80 °C[5] finally afforded (+)-goniodiol (**1**) {98%, $[\alpha]_D = +72 \times 10^{-1}$ deg cm^2 g^{-1} (*c* 0.3), lit.[2] $[\alpha]_D = +74.4 \times 10^{-1}$ deg cm^2 g^{-1} (*c* 0.3, $CDCl_3$)} the ^1H and ^{13}C NMR spectral data for which matched those reported previously.[2,5] Analogous deprotection of compound **15** gave 6-*epi*-(+)-goniodiol **16** {85%, $[\alpha]_D = -47 \times 10^{-1}$ deg cm^2 g^{-1} (*c* 0.3)}.

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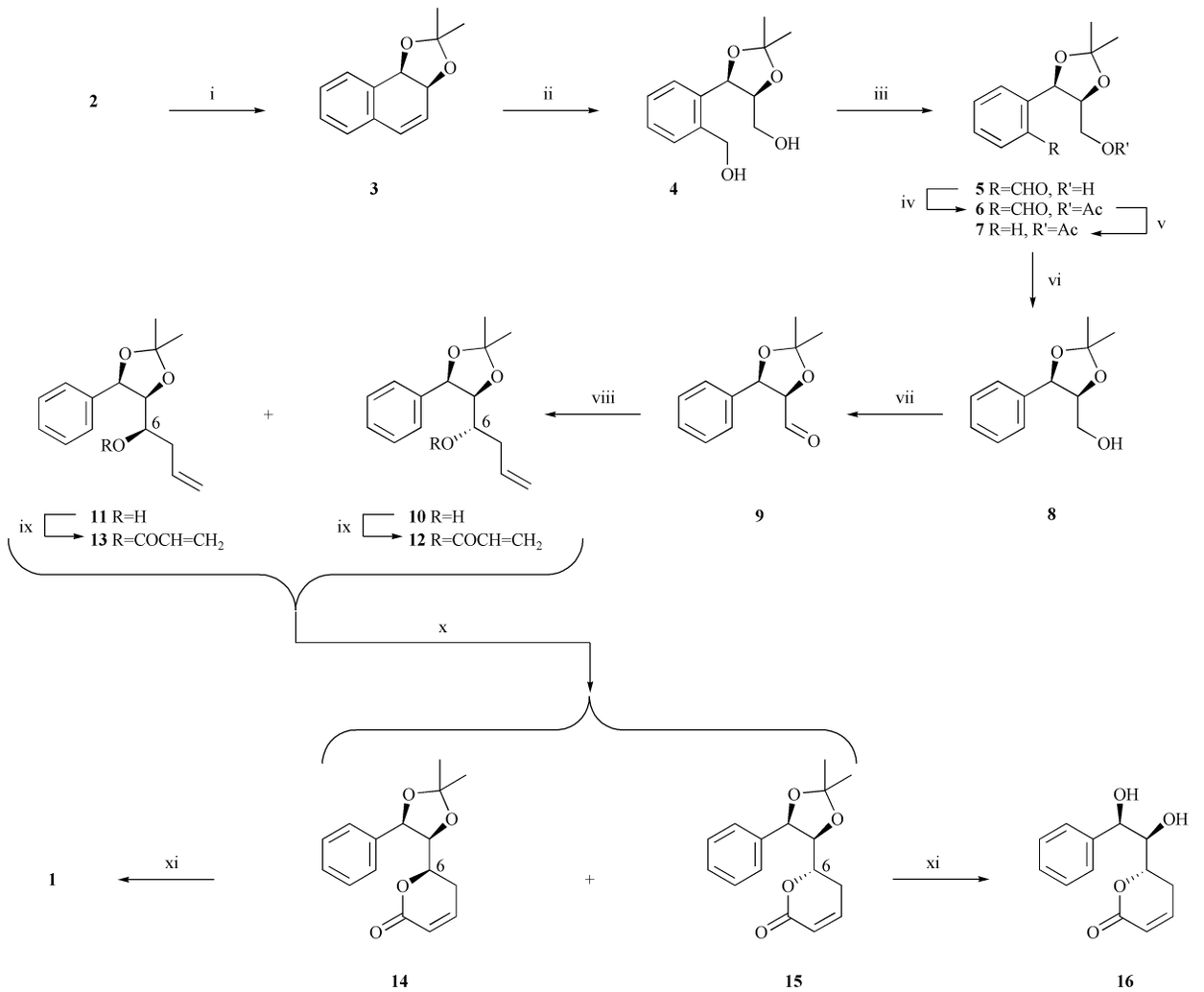

Scheme 1 *Reagents and conditions*: (i) 2,2-DMP, *p*-TsOH (cat.), 18 °C, 1.5 h; (ii) (a) OsO_4 (10 mol%), 3 : 1 v/v DME–H_2O, 18 °C, 0.25 h then $NaIO_4$ (3 mol equiv.), 18 °C, 15 h; (b) $NaBH_4$ (4 mol equiv.), MeOH, 0 °C, 2 h; (iii) MnO_2 (20 mol equiv.), DME, 18 °C, 3 h; (iv) Ac_2O (6 mol equiv.), DMAP (cat.), pyridine (6 mol equiv.), DCM, 18 °C, 2 h; (v) $[Rh(dppp)_2]^+BF_4^-$ (10 mol%), xylene, *ca.* 140 °C, 15 h; (vi) K_2CO_3 (10 mol equiv.), MeOH, 18 °C, 0.25 h; (vii) NMO (1.7 mol equiv.), TPAP (17 mol%), powdered 4 Å molecular sieves, DCM, 18 °C, 0.66 h; (viii) $H_2C{=}CHCH_2SnBu_3$ (3 mol equiv.), $LiClO_4$ (5 M in Et_2O), 18 °C, 4 h; (ix) acrylic anhydride (20 mol equiv.), DMAP (40 mol equiv.), THF, −20 to 18 °C, 16 h; (x) $(Cy_3P)_2Cl_2Ru{=}CHPh$ (10 mol%), DCM, 18 °C, 4 h then DMSO (10 mol equiv.), 18 °C, 16 h; (xi) 1 : 1 v/v AcOH–H_2O, 80 °C, 0.5 h.

Experimental

Compound 7

Degassed xylene (1 mL) was added to a mixture of aldehyde **6** (165 mg, 590 μmol) and bis[1,3-bis(diphenylphosphino)-propane]rhodium tetrafluoroborate (63 mg, 10 mol%) maintained under an atmosphere of nitrogen. The ensuing mixture was stirred magnetically whilst being heated at reflux for 15 h. The cooled reaction mixture was filtered through a pad of Celite™ which was washed with ether (5 mL). The combined filtrates were concentrated under reduced pressure and the resulting brown oil subjected to flash chromatography (silica, 1 : 4 ethyl acetate–hexane elution) and thereby yielding two fractions, A and B.

Concentration of fraction A (R_f 0.25) gave the starting aldehyde **6** (59 mg, 36% recovery) which was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f 0.40) gave the *title compound* **7** (71.4 mg, 76% yield at 64% conversion) as a white crystalline solid, mp = 65–68 °C, $[\alpha]_D$ -109×10^{-1} deg cm² g^{-1} (*c* 1.1) (Found: C, 67.1; H, 7.2. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.3%). ν_{max} (KBr)/cm^{-1} 1735, 1376, 1237, 1212, 1087, 1033, 983, 752 and 704; δ_H (300 MHz, $CDCl_3$) 7.38–7.30 (5H, complex m), 5.32 (1H, d, *J* 6.9 Hz), 4.56 (1H, ddd, *J* 8.0, 6.9 and 4.4 Hz), 3.71 (1H, dd, *J* 11.7 and 4.4 Hz), 3.61 (1H, dd, *J* 11.7 and 8.0 Hz), 1.92 (3H, s), 1.65 (3H, s), 1.49 (3H, s); δ_C (75 MHz, $CDCl_3$) 170.8, 136.3, 128.7, 128.5, 126.7, 109.5, 78.7, 76.5, 64.5, 27.6, 25.2, 20.9; *m*/*z* (EI) 250.1205 ($M^{+\bullet}$, $C_{14}H_{18}O_4$ requires 250.1205, 0.4%), 235 (25), 192 (19), 148 (100), 133 (82), 119 (61), 101 (78), 91 (68).

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Notes and references

† The IUPAC name for mandelic acid is phenylglycolic acid. The IUPAC name for glycidol is 2,3-epoxypropan-1-ol.

‡ All new and stable compounds had spectroscopic data [IR, NMR, mass spectra] consistent with the assigned structure. Satisfactory combustion and/or high-resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

§ All optical rotations were determined in a chloroform solution at 20 °C unless otherwise specified.

¶ The assignment of stereochemistry at C-6 (goniodiol numbering) in products **10** and **11** follows from their conversions into 6-*epi*-(+)-goniodiol (**16**) and (+)-goniodiol (**1**), respectively.

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